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Comorbidity of Anxiety and Affective Disorders as Neuropsychiatric and Evolutionary Problem (A New Concept)

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1. Introduction

Although the comorbidity issues in psychiatry have received a wide recognition for at least the last 20 years and caused a great stream of publications all over the world, many questions remain unanswered. It concerns as phenomenon of comorbidity itself, as plausible explanation of its origin. Little is known, why in some patients the so-called pure (non comorbid) psychopathological states present (i.e. pure depression or anxiety), while in other cases comorbidity between affective and anxiety disorders exists. At present, factors determining the comorbidity between depression and anxiety disorders unfortunately remain unknown.

The principal and unexplained phenomenon in comorbidity issues concern the asymmetry in comorbidity between affective and anxiety disorders (Table 1). Indeed, patients with primary diagnosis of anxiety disorder have more frequent comorbidity with depression (48-62%) than vice versa (10-20%, Table 1). (Kendler et al., 1992; Kessler, 1999; Kessler et al., 1994; 1995; 1996, 1999; Roy-Byrne et al., 2000).

These findings haven't obtained any plausible explanation yet, and comorbidity studies including description of comorbid disorders and statistical evaluation of risk for their development didn't give us any clue (except for genetic origin or predisposing trigger factors) for solving these issues.

On the other hand, neuropsychological or neuropsychiatric mechanisms have been rarely used in order to explain any psychopathological phenomena, and strong demarcation line, unfortunately still exists between neuropsychology and general psychopathology, although the both disciplines represent two domains of neuroscience. It concerns the problems of localization and lateralization of cerebral functions as in so-called normal, as in pathological states, although a great progress has been achieved for the last forty years in realms relevant to these problems. Moreover, epilepsy (especially temporal lobe epilepsy, TLE) seems to represent a useful model for profound understanding of unresolved psychopathological issues, including comorbidity between anxiety and depression.

In the present article an attempt has been made on suggestion one of possible mechanisms for comorbidity development based on neuropsychiatric and evolutionary data, although suggested paradigm, may be criticized and appraised rather as speculative due the lack of direct and strong evidence based data relevant strictly to comorbidity of affective and anxiety disorders.

2. The prevalence of affective and anxiety disorders and asymmetry in their comorbidity

The principal fact should be stressed, that in general population affective disorders in form of depression occur more frequently than anxiety disorders (Table 2).

AD	Prevalence in population	Probability for coincidence with MDD	Comorbidity1 (of MDD with AD)	Comorbidity2 (of AD with MDD)	Ratio of Co-moridity1 to probability for coincidence	Ratio of Co-moridity2 to probability for coincidence
PD	3,4% [2]	0,58%	9,9% [21,24]	55,6% [2]	17,1	95,9
GAD	4 - 6% [44, 45]	0,68-1,02%	17,2% [21,24]	62% [17, 21,22]	16,9 - 25,3	60,8 - 91
PTSD	1,3 -8,4% [45]	0,22- 1,42%	19,5% [21,24]	48% [23,24]	13,7 - 88,6	33,8 - 218

Notes: the lifetime prevalence of MDD according to data by Blazer et al. (1994) consists 16,9%. Comorbidity 1 implies the primary diagnosis of MDD; Comorbidity 2 - the primary diagnosis of AD.

Table 1. Asymmetry in comorbidity between depression and anxiety, lifetime comorbidity of MDD with AD, and lifetime co-morbidity of AD with MDD and calculated variables for co-morbidity probability

Ratios of Comorbidity 1 and Comorbidity 2 to probability for chance expectation show the magnitude of comorbidity level relatively to chance coincidence.

The data on prevalence of affective disorders and anxiety are well known and have been reported in numerous publications performed mostly by Kessler (1999) and Kessler et al.(1994; 1995; 1996, 1999). The principal data on comorbidity of affective and anxiety disorders are listed in the table 1. This table has been created based on literature findings relevant to prevalence of depression and anxiety and their concomitant existence in general population (Eaton et al., 1994; Kessler, 1999; Kessler et al., 1994, 1995, 1996, 1999; Judd et al., 1998).

Authors	Amount of studied patients	Prevalence of affective disorders (%)	Prevalence of anxiety disorder (%)	Significance of discrepancies
Strine et al., 2005	30018	15,5%	6,8%	p=0,00001
Tellez-Zenteno &Wiebe, 2005	36984	10,8%	4,7%	p=0,00001
Kobau et al., 2006	4151	15%	15%	n.s.
Total	71153	13,8%	8,8%	p=0,00001

Table 2. Comparison of prevalence of affective (depressive) and anxiety disorders in general population

As can be seen from table 1 there are certain discrepancies in variables “Comorbidity 1” and “Comorbidity 2”: the “Comorbidity 1” is 2 – 5,5 fold lower, then “Comorbidity 2” level. In other words, the primary and main diagnosis of MDD has caused lower level of comorbidity with any AD, while the primary diagnosis of AD has lead to higher level of comorbidity with MDD, and the last category seems to be more consistently present in comorbid pairs, than AD. These data were firstly revealed by Kessler (1999) and depression itself seems to be more universal and frequent phenomenon in comorbidity than anxiety. At the first glance the cause for such discrepancy remains unclear, although such an asymmetry may be explained partly by more frequent occurrence of pure depressive disorders compared with pure anxiety disorders, and data depicted in tables 2, as a rule, confirm this suggestion.

A genetic loading alone isn't able explain such an asymmetry in comorbidity. If anxiety and depression were regarded as manifestations of one disease with shared genetic inheritance in such a case there could be a symmetry in comorbidity between them and level of comorbidity should approach at least to 1,0 (100%), but this isn't the case.

On the other hand, depression and anxiety can't be regarded as independent phenomena since in this case the comorbidity level should be much lower (as can be seen in second column) than the real data on comorbidity between them.

The question on a temporal sequence in the development of MDD and AD hasn't also received a proper answer, although it seems to be the principal one. Once again we aren't able to explain the real level and asymmetry in comorbidity dependent on main and primary diagnosis. The psychodynamic point of view has been proposed by Wittchen et al. (1994, 2003). According to this scheme, depression develops as secondary disorder to primary anxiety disorder. The last has appeared earlier than former and plays a causal role for depression development. Although such an opinion has become a dominant and widespread, the mentioned model has been obtained mainly on patients with social anxiety and simple phobia, while data on persons with PD or GAD can't be incorporated in aforementioned scheme, because these anxiety disorders are thought to appear in later age (Wittchen et al., 1994; 2003; Baldwin, 2003; Baldwin & Polkinghorn, 2005). It concerns particularly GAD, which age at onset is believed to be at average between 35 and 45 years (Baldwin, 2003; Baldwin & Polkinghorn, 2005). On the other hand, an average age at onset for recurrent depression seems to be younger, and in the Epidemiologic Catchment Area Study has been shown that in subjects who developed a major depressive episode, 20% had initial symptoms by age 19 and subsequently developed a major depressive episode by age 25, while 50% showed depressive features by age 26 and developed depressive episode by age 39 (Rehm et al., 2004). The age of onset for panic disorder, as a rule, coincident with major depression and seems to be in interval between middle to late 20 years (Anderson et al., 1984; Rapee, 1985; Rapee & Barlow, 2004).

Moreover, the so-called simple and social phobia may be regarded as features in the frame of premorbid personality in persons with prevailed anxiety and obsessions. In this context suggestion could be made that such premorbid personality with excessive worries and sense of debt is very similar to *Typus melancholicus* described by Tellenbach (1971). This personality structure is thought to be a risk factor for sequential development of MDD, although not all studies could confirm this rule.

Obviously the mentioned above psychodynamic mechanism alone would not be enough to explain properly the cause of comorbidity between affective and anxiety disorders.

Moreover, such a possible mechanism isn't able again to explain the asymmetry in comorbidity between MDD and AD.

At last, data in last two columns (ratio of Comorbidity 1 and Comorbidity 2 to values of probabilities for chance coincidence MDD and respective AD) show the certain discrepancies between these two ratios. Thus, the probability for comorbidity of primary MDD diagnosis with any AD is 14 - 90 times higher, while for comorbidity of any primary AD diagnosis with MDD is 30 - 218 times higher, compared with chance expectation for two disorders. Once again the ratio values for Comorbidity 2 are 3-5 times higher, than for Comorbidity 1. It means that in the occurrence of any AD the presence of MDD is much more probable, than vice versa. In other words, in the case of primary diagnosis of any AD the appearance of MDD is much more inevitable than in cases of primary diagnosis of MDD, although the plausible explanation for such a discrepancy is still absent. Obviously this can be explained by earlier MDD beginning that precedes the onset of AD, but not vice versa. It concerns strictly the diagnosis of GAD and in less degree the diagnosis of PD, but not the diagnosis of simple and social phobia that begin usually earlier than MDD (Kessler, 1999, Wittchen et al., 2003).

Moreover, the age at onset for MDD after primary beginning of AD is at average 11,2 years higher, than vice versa (i.e. if MDD precedes the onset of AD, as has been shown in National Comorbidity Survey (Kessler, 1999). It concerns mostly for all forms of phobias and Posttraumatic stress disorder, but not PD and GAD (Kessler, 1999). Probably such discrepancy may be explained by more prominent role of genetic factors for primary MDD development, whilst in cases of secondary MDD and primary AD diagnosis the involvement of environmental and psychogenic factors may be more important especially for depression development.

3. The cerebral locus as cause for psychopathology (with emphasis on hemispheric laterality in affective and anxiety disorders)

The data relevant to local cerebral pathology as possible cause for psychopathological signs, unfortunately, are scarce, controversial and have not received yet a proper appraisal. All such findings were obtained, as a rule, on neurologically ill patients, but not in persons with so-called functional disorders, including major depressions and different anxiety disorders. Among neurological diseases more frequently were studied epilepsy, traumatic brain injury, cerebral tumors with psychopathological manifestations, Parkinson's disease, multiple sclerosis and stroke.

In line with main objective of present article the data on affective (depressive) and anxiety symptoms are present without concern other psychopathology.

Numerous data have shown that in patients with stroke the side of damage plays role in depression origin, although all findings remain mostly controversial. Thus, in series of trials, performed by Robinson (2000) and Robinson & Szelata (1981), Robinson et al. (1984) has been shown that in patients with left hemisphere stroke the major depression developed in 60% with lesion in the frontal region, and in 13% with lesion in posterior region. On the contrary, in patients with right hemisphere stroke depression was revealed in 17% lesion in posterior region and in none case in anterior region. It implies that patients with left anterior lesion have significantly higher probability for major depression development than patients with any other lesion location (Robinson, 2000; Robinson et al., 1984).

Moreover, the proximity of lesion to the frontal pole in the left hemisphere occurs to correlate with severity of depression: the closer the lesion to the frontal pole is located the more severe degree of depression is expected. For the right hemisphere strokes such an association hasn't been revealed, and quite the contrary, the closer the lesion is located to posterior pole the more severe depression is observed (Robinson, 2000; Robinson & Szetela, 1981). Such a mirror image relationship between depression and lesion locations seems to point to two different depressive syndromes, which perhaps despite their external similarity, nevertheless, might have hidden discrepancies in their psychopathological symptoms, although this should be proved in a special study.

Moreover, these data fairly consist with Geodakian's paradigm on evolutionary stages of any signs development: old and even ancient signs are affined to posterior brain regions and right hemisphere, while new (recently acquired) signs have affinity to frontal brain regions and left hemisphere (1993).

Another interesting findings, obtained in studies by Robinson (2000) and Starkstein and Robinson (1989) concern the role of family psychiatric history among patients with major depression following right hemisphere stroke. Principally, the similar family loading on psychiatric disorders in patients with left hemisphere lesions hasn't been found (Starkstein and Robinson, 1989). This might suggest the different vulnerability for depression development in patients with left and right hemisphere stroke due genetic factors. Patients with depression after right hemisphere stroke seem to be more prone to depression, which in evolutionary terms is older and determined rather more by genetic and less environment factors than depression in patients with left hemisphere stroke, although an external psychopathological similarity should be in both subtypes.

Data on anxiety states due focal brain lesions are less consistent and were observed less frequently. Nevertheless, anxiety is thought to represent the second most prevalent mood disorder after depression in stroke patients, and its prevalence is believed to reach 3,5-24% of all stroke patients (Starkstein et al., 1990; Astrom, 1996). So-called pure anxiety syndromes are thought to occur more frequently in patients with right hemisphere lesions, while anxiety with concomitant depression occurs in persons with left hemisphere strokes (Astrom, 1996; Castillo et al., 1993; Ghika-Schmid & Bogousslavsky, 2000).

Data on interictal anxiety in temporal lobe epilepsy (TLE) are more controversial. Thus, according to data by Dobrochotova & Bragina (1977) depression frequently prevails in patients with right sided foci while in patients with left sided foci, as a rule, more frequently anxiety occurs than depression. Here should be stressed that these data were obtained analyzing the aura semiotics in patients with epilepsy and cerebral tumors, and in this context these data may be not properly comparable with mentioned above findings, since data obtained rather in patients with depression or anxiety states in interictal period are required.

Interestingly, the data by Altshuler et al. (1990) and Perini and Mendius (1984) obtained on patients with TLE in interictal period are consistent with mentioned findings. In their study anxiety disorders were registered more frequently in patients with left than right-foci epilepsy. Similarly, in study by Kalinin and Polyanskiy (2009) the frequency of diagnosis of organic anxiety disorder in TLE patients with left-sided focus was 3 fold higher than in patients with right-sided focus. On the contrary, in the last subgroup of patients more frequent was the diagnosis of organic affective disorder. In other words, in interictal period in patients with TLE the right focus activity determines mainly affective disorder (depression), while the left focus epileptic activity, conversely, provokes anxiety disorder.

In study by Helmstaedter et al. (2004) the inverse correlations between Beck Depression Inventory score and verbal learning, verbal recognition and figural learning strictly for left lateral temporal lobe epilepsy were obtained, that confirms the significance of foci lateralization for depression development. Interestingly, statistically significant correlations between Depression score and temporal lobe epilepsy with right foci (irrespective of mesial or lateral) and left mesiotemporal lobe epilepsy were absent. It confirms the significance of left lateral temporal foci strictly in the development of depression and cognitive impairment in cases of neocortical, but not mesiotemporal epilepsy. In other words, the depression associated with cognitive impairment originates mostly in persons with neocortical epilepsy and left-sided foci only. Nonetheless, depression can also occur in patients with mesiotemporal epilepsy but irrespective of the foci lateralization, as has been shown in study by Quiske et al. (2000). The authors evaluated the association of MRI-defined mesiotemporal sclerosis (MTS) with Beck Depression scores in 60 patients with temporal lobe epilepsy. Mean depression score was significantly higher in patients with MTS, irrespective of MTS lateralization, and investigators concluded, that depression is a good indicator of MTS, but not vice versa. However in such a case the link between depression and cognitive deterioration is absent (Quiske et al., 2000). It implies that depression may occur irrespective of side foci in paleocortical epilepsy, but predominantly in case of left-sided foci in neocortical epilepsy. Obviously, in evolutionary terms depression in patients with mesiotemporal epilepsy seems to be older compared with depression in persons with neocortical epilepsy.

From evolutionary point of view these findings are consistent with data on depression in stroke patients and stress the significance of left hemisphere lesion (focus) for origin of relatively novel depression combined with cognitive deterioration in evolutionary terms. Nevertheless, the possibility for depression development in patients with right foci (lesions) also couldn't be excluded, but in such a case so - called evolutionary age of depression would be more ancient. In other words, such depression should have earlier age of onset, and probably the lack of cognitive impairment than depression associated with left hemisphere, although this again should be proved in special trials.

In summary, the aforementioned data have showed the possibility for neuropsychological and evolutionary approach at the same time to anxiety and depression involvement in patients with epilepsy and stroke. Such an approach itself at first glance is not relevant enough to comorbidity problems of affective and anxiety disorders at all. Nonetheless, the possibility exists to extrapolate such approach on comorbidity issues of anxiety and affective disorders too, because certain brain functions *a priori* must be considered as universal for all cerebral disorders and diseases.

4. Asymmetry in neuropsychological tests for verbal and gestalt function in patients with epilepsy

A great deal of data exists that contradict to traditional knowledge of the role the left and right hemispheres in neuropsychological functions processing. Thus, the classical and traditional point of view on distribution of cerebral functions asserts the primary role of left hemisphere in verbal and analytical functions, and right hemisphere in so-called gestalt functions including visual and spatial cognition. Based on this paradigm suggestion can be made, that temporal lobe epilepsy (TLE) with left-sided foci should cause strictly damage of verbal memory and analytical abilities, while in right-foci TLE an impairment in

visuospatial tests should be expected (Lavadas et al., 1979; Mungas et al., 1985; Ossetin, 1988).

The findings obtained after selective left- or right temporal lobes had been removed, as a whole, confirmed aforementioned paradigm (Milner, 1965).

This traditional view had steadily existed until the recent years when principally new findings were obtained on patients with TLE. Thus, statistically significant relations between foci lateralization and impairment of verbal and nonverbal memory have been revealed not in all studies (Perrine & Kiolbasa, 1999; Spencer, 1998), that can't be solely explained by traditional paradigm of discrepancies in left- and right hemisphere functions. Proposed explanations usually were based on facts of bilateral temporal lobes involvement in cases of mesiotemporal epilepsy (Dupont, 2002; Dupont et al., 2002). In such cases there is no need to contrast left- and right foci in patients with TLE, since hippocampal sclerosis is thought to cause damage as in the left, as in the right temporal lobe.

Nevertheless, the data on differences in capability of left and right hemispheres in neuropsychological test performing by patients with TLE have been observed not only in epilepsy with hippocampal sclerosis, but in cryptogenic epilepsy too.

Thus, in study by Moore and Baker (1996) Wechsler tests for evaluating verbal, visual and general memory were used in patients with TLE resistant to antiepileptic drugs. The patients with left foci performed tests on verbal and logic memory worse, than patients with right foci, as should be expected. Nevertheless statistically significant differences in nonverbal and visual tests between patients with left and right foci haven't been obtained. It implies that nonverbal and visual functions are determined not only by right hemisphere but by left hemisphere too. The similar findings have been also obtained in other studies (Barr & Consortium, 1995; Breier et al., 1996).

Notably, the similar results are observed irrespective of epilepsy form, i.e. as in cryptogenic, as in symptomatic temporal lobe epilepsy (Giovagnoli & Avanzini, 1999). In other words, the brain organic lesion itself, including mesiotemporal sclerosis, isn't enough to explain aforementioned discrepancies in hemisphere functions. The left hemisphere seems to be responsible as for analytic and verbal, as for gestalt function, while the right hemisphere – strictly for gestalt functions. Based on their findings authors concluded that lateralization of brain functions concerns strictly the verbal, but not the visual functions (Giovagnoli & Avanzini, 1999).

Concluding this part of article we may suggest that TLE with left foci is more virulent than with right foci, because it causes deterioration as in verbal, as in nonverbal functions. In this context epilepsy with left foci is quite similar to epilepsy with bilateral foci, and discrimination between them based solely on clinical data seems to be difficult. On the other hand, the right-foci epilepsy seems to be characterized strictly by unilateral damaged functions, determined by the right hemisphere. Any adequate explanations for these discrepancies are still unfortunately absent, but suggestion can be made that part of left hemisphere functions duplicates the properties of right hemisphere in temporal lobe epilepsy. Obviously, an extrapolation from epilepsy model on other pathological states and disorders are probable, since brain mechanisms concerning hemispheric laterality function must be universal.

5. An evolution of brain functions in phylogeny and ontogeny

Ernst Haeckel, a brilliant German biologist and successor of Charles Darwin, had discovered in 19-th century rule, which later has become known under his name as biogenetic law

(Haeckel, 1870). According to this law, the temporal sequence of acquired characteristics in ontogeny is quite similar to that in phylogeny in condensed manner. In other words, the appearance of any signs, symptoms, disorders, and pathology, at all, during individual life repeats its appearance in phylogeny for this species. Based on this rule, the prediction can be made, that earlier appearance of signs and disorders in ontogenesis of *Homo sapiens* reflect their earlier origin in evolution while the appearance of any signs in later period of individual life points out to the novel evolutionary signs.

The further development of Haeckel' law has been made by modern Russian biologist V. Geodakian (1993) , who has extrapolated Haeckel's rule on brain evolution taking into account the role of cerebral lateralization.

In line with Geodakian's rule, the hemispheric lateralization of different cerebral functions also points at different time period for their appearance in phylogeny. Thus, the right hemisphere is responsible for gestalt analysis, and is regarded as ancient brain function, while the left hemisphere, conversely, determines the analytical and verbal processing, that are thought to be the novel acquired brain functions (Geodakian, 1993).

The similar point of view on the cerebral lateralization as indicator of acquired brain functions at different stages of evolution of *Homo sapiens* has been reported by other authors, and particularly by British psychiatrist Timothy Crow (1998).

Taking all these data together, a suggestion can be made, that any characteristics and symptoms in neuropsychiatric disorders associated with left hemisphere should be regarded as younger in comparison with signs and symptoms associated with right hemisphere (Geodakian, 1993; Crow, 1998). In addition, the appearance of right hemisphere signs (i.e. syndromes and disorders) in ontogenesis has to occur earlier than appearance of signs determined by left hemisphere. Nevertheless, in development of certain cerebral disorders the existence of some symptoms and syndromes attributed to left hemisphere is thought to imply the earlier existence of similar signs connected to the right hemisphere, and data discussed above, as a whole, confirm this hypothesis. On the other hand, a definite functions and signs existed that are attributed strictly to left hemisphere (i.e. analytical and verbal functions) but not *vice versa*. In other words, right hemisphere functions seem to be less universal and specific than some functions determined by left hemisphere. If accept that hypothesis, then data on asymmetry in test performance in epileptic patients described in previous chapter can simply be explained: the functions of left hemisphere mean not only verbal and analytical processing, but visual and dimensional too. On the contrary, the functions of right hemisphere seem to be restricted for gestalt analysis. Obviously, the mentioned gestalt functions appear earlier in the right hemisphere and later in the left hemisphere. This explains why a damage of right hemisphere can cause impairment of gestalt processing only, while the damage of left hemisphere leads to impairment of both analytical and verbal, and gestalt processing. At last, if take into account the psychopathological symptoms or syndromes, attributed electively to the left or the right hemisphere, then we may presume that existence of some left hemisphere psychopathological signs imply the existence of similar signs in the right hemisphere in earlier stage of ontogenesis, but not *vice versa*. The left hemisphere seems to be much more functionally capable, than right hemisphere, although this remains a pure speculative suggestion.

Obviously, localization data also should be considered in evolutionary model along with lateralization findings. Here should be reminded a well known scheme, that brain evolution has direction from posterior to anterior regions (i.e. from occipital and parietal lobes to temporal, and from them to frontal lobes). Frontal lobes seem to be the youngest regions of brain in evolutionary terms.

6. Hemispheric and evolutionary hypothesis for comorbidity

In the previous sections of current article an unequal role of left and right hemispheres in certain neuropsychological test has been revealed, and evolutionary approach for explanation in asymmetry in test results has been proposed. As has been shown the left hemisphere is much more capable in test performing (including not only verbal, but gestalt functions too) compared with right hemisphere which functions are restricted entirely to gestalt analysis.

Obviously, the left hemisphere in someway duplicates the functions and properties of right hemisphere (which have earlier origin in ontogenesis) and by that possesses more functional variability, than right hemisphere. If accept this hypothesis and extrapolate that to all functions and properties of brain (with emphasis on psychopathological symptoms and syndromes), then data on comorbidity between affective and anxiety disorders may be explained from proposed above point of view.

Really, a certain parallelism between neuropsychological tests performing in epileptic patients and affective and anxiety symptoms development due isolated cerebral hemisphere lesion can be seen, although there are data, that in someway contradict to this paradigm. Nevertheless, depression may be evolved due as the right, as the left hemisphere involvement, and existence of left hemisphere pathology (either depression, or anxiety) implies the previous existence of hemisphere pathology (mostly in the form of depression). In other words, the more variable and broad functions of left hemisphere not only in neuropsychological tests but a greater variability in all properties is seen. It concerns, particularly, affective and anxiety symptoms and syndromes. As has been shown above the left hemisphere is involved in depression and anxiety genesis and by that determines presumably comorbidity between them. Moreover, an asymmetry in comorbidity levels between depression and anxiety may be explained if accept, that pure anxiety syndrome is more attributed to left, than right hemisphere, although this rule has been confirmed only in several studies (Dobrochotova & Bragina, 1977; Altshuler et al. 1990); Perini and Mendius, 1984; Kalinin & Polyanskiy, 2009). Conversely, in cases of isolated involvement of the right hemisphere and depression existence the left hemisphere may remain intact. This explains more frequent prevalence of depression over anxiety disorders. All data discussed above also could confirm this suggestion.

Obviously, the existent data are not enough to accept a hypothesis proposed above entirely. Nevertheless, in cases of left hemisphere involvement the concomitant appearance of both depression and anxiety has been observed, that is consistent with mentioned hypothesis.

On the other hand, the mixed and poorly differentiated depressive and anxiety states were registered more frequently in TLE patients with right hemisphere focus. Moreover in such TLE patients the so-called alexithymic features in premorbid period are strongly expressed, and alexithymia complemented to the right-sided focus seems to be a risk factor for depression or anxiety development (Kalinin et al., 2010).

As phenomenon, anxiety is characterized by higher degree of cognitive processing and vigilance in comparison with depression that, in turn, implies the left hemisphere involvement in anxiety disorders. Moreover, traditionally anxiety is thought to be divided on psychic subtype and somatic subtype, and the former is more attributed to left hemisphere, while the somatic anxiety is thought to be attributed to the right hemisphere. Several observations confirm this suggestion. Thus, Reiman et al. (1984, 1986) found PET abnormalities in the right parahippocampal region in patients with panic disorder. Similarly

Fontaine et al. (1990) revealed MRI abnormalities in the right temporal lobe, while Nordahl et al. (1990) reported asymmetric blood flow in the parahippocampal gyrus in patients with panic disorder, attributed to greater increase on the right side. Taking all these data together, conclusion can be made, that involvement of the right temporal lobe or parahippocampal region may be important to the development of panic attacks. Noteworthy, the panic attacks include also symptoms of depression, and are characterized by more pleomorphic psychopathological structure compared with psychic anxiety in GAD.

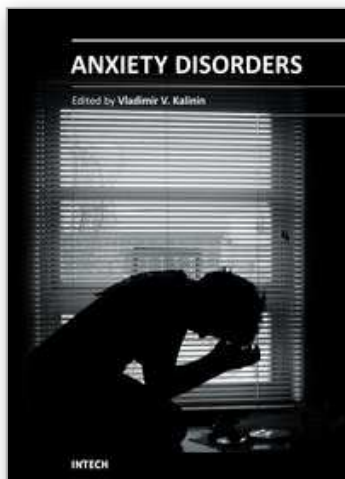
In conclusion, the current evolutionary and neuropsychiatric approach to comorbidity issue in psychiatry is seen to remain as pure speculative due the lack a necessary amount of evidence based data. Nevertheless, if assumption on unequal frequency of depression and anxiety attributed to right and left hemisphere could be proved, then a rule explaining comorbidity would be formulated: in cases of primary diagnosis of so-called relatively novel in evolutionary terms disorders (attributed to left hemisphere) the greater frequency of comorbid disorder is expected, which is older in evolutionary terms. On the contrary, in cases of primary diagnosis of relatively old disorder (attributed to right hemisphere) the frequency of comorbid novel disorders is probably much less. Certainly, such a rule remains pure speculative hypothesis and must be proved or refuted in special studies in the future.

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During the last 2-3 decades drastic research progress in anxiety issues has been achieved. It concerns mostly the study of different subtypes of anxiety and their treatment. Nevertheless, the data on anxiety pathogenesis is less elaborated, although here a multidimensional approach exists. It includes neurochemistry, pathophysiology, endocrinology and psychopharmacology. Again, we are able to recognize the multifarious sense of anxiety, and the present collective monograph composed of 16 separate chapters depicting the different aspects of anxiety. Moreover, a great part of book includes chapters on neurochemistry, physiology and pharmacology of anxiety. The novel data on psychopathology and clinical signs of anxiety and its relationship with other psychopathological phenomena is also presented. The current monograph may represent an interest and be of practical use not only for clinicians but for a broad range of specialists, including biochemists, physiologists, pharmacologists and specialists in veterinary.

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